IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

REGENXBIO INC. and THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA,	)	
Plaintiffs,	)	C.A. No. 20-1226 (RGA)
v.	)	REDACTED - PUBLIC VERSION
SAREPTA THERAPEUTICS, INC. and SAREPTA THERAPEUTICS THREE, LLC,	)	
Defendants.	)	

DEFENDANTS' OPENING BRIEF IN SUPPORT OF THEIR MOTION FOR SUMMARY JUDGMENT AND TO EXCLUDE EXPERT OPINIONS

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I. INTRODUCTION

Plaintiffs have a failure of proof on infringement. Plaintiffs' technical expert, Dr. Leone, identifies a list of narrowing criteria that she contends must be satisfied before an adeno-associated virus ("AAV") sequence falls within the scope of the Asserted Claims. Dr. Leone relies on these criteria in her rebuttal report on validity to argue that the Asserted Claims, narrowly construed, are described and enabled. However, Dr. Leone does not include these criteria in her opening report on alleged infringement. She offers no opinion that Sarepta's sequences satisfy any of these criteria or infringe the Asserted Claims as she has construed them narrowly to avoid invalidity. The only proffered evidence on this issue is the unrebutted opinion of Sarepta's technical expert, Dr. Kay, that when Dr. Leone's criteria are applied, Sarepta's sequences do not infringe. Without expert testimony applying Dr. Leone's criteria to the sequences in Sarepta's accused cultured host cells, Plaintiffs cannot meet their burden on infringement, and summary judgment is warranted.

Further, the Asserted Claims are not patent-eligible subject matter under 35 U.S.C. § 101. It is undisputed that the AAV sequences recited in the Asserted Claims are naturally occurring – and therefore, not patentable. Indeed, the named inventors touted their contribution to the art as the isolation of AAV sequences obtained from natural sources. It is also undisputed that, at the time of the '617 patent, it would have been well within the knowledge and ability of a person of ordinary skill in the art ("POSA") to make and use a "cultured host cell" containing a "recombinant nucleic acid molecule" encoding a naturally occurring AAV sequence. As such, the additional elements recited in the Asserted Claims add nothing inventive to the naturally occurring AAV sequences. Thus, the Asserted Claims are invalid for lack of patent-eligible subject matter, and summary judgment is warranted for this additional reason.

Next, the opinions of Plaintiffs' damages expert, Dr. Heeb, are unreliable and contrary to established authority: (1) Dr. Heeb's analysis violates the Entire Market Value Rule because his

opinions are based on the projected profits on future sales of Sarepta's SRP-9001 gene therapy product, without the required showing that the patented technology drives demand. Indeed, Dr. Heeb uses projected profits for SRP-9001 as his royalty base, even though Plaintiffs have argued throughout this case that Sarepta's final products are not accused of infringement. (2) Dr. Heeb also relies on product development agreements that he has made no attempt to show are technically or economically comparable to the license at the hypothetical negotiation, as he is required to do. (3) Finally, Dr. Heeb relies on theoretical bargaining methods that are untethered to the value of the accused cultured host cells and the specific facts of this case, in violation of established Federal Circuit precedent. For all these reasons, Dr. Heeb's damages opinion should be excluded.

Finally, the opinions of Plaintiffs' technical expert, Dr. Leone, on issues of indirect infringement are unreliable and should be excluded. Dr. Leone has no expertise that would assist the jury on issues relating to Sarepta's knowledge of the asserted patent or alleged intent to infringe – issues that are well within the purview of the jury to decide based on its own assessment of the evidence, without second-hand commentary from a technical expert.

II. NATURE AND STAGE OF THE PROCEEDINGS

Plaintiffs allege that Sarepta infringes claims 1-9, 12, 15, and 18-25 ("the Asserted Claims") of U.S. Patent No. 10,526,617 ("the '617 patent"). Ex. 2 at 2; Ex. 3 at 2. Fact and expert discovery are closed, and trial is scheduled for January 29, 2024. D.I. 44.

III. SUMMARY OF ARGUMENTS

1. It is axiomatic that claims must be construed the same way for purposes of infringement and validity. *Amazon.com, Inc. v. Barnesandnoble.com, Inc.*, 239 F.3d 1343, 1351 (Fed. Cir. 2001). Here, in order to avoid invalidity, Plaintiffs' expert, Dr. Leone, contends that the AAV sequences falling within the scope of the Asserted Claims must meet certain, specified criteria. However, in her analysis of alleged infringement, Dr. Leone offers no opinion that the

sequences in Sarepta's accused cultured host cells satisfy the same criteria that she says are required by the Asserted Claims for validity. Dr. Leone has no rebuttal to the opinions of Sarepta's expert, Dr. Kay, that when Dr. Leone's criteria are applied, Sarepta's sequences do not infringe. Thus, Plaintiffs have a failure of proof on the issue of whether the sequences in Sarepta's accused cultured host cells infringe the Asserted Claims, an issue on which they bear the burden.

2. The Asserted Claims are not eligible for patenting under 35 U.S.C. § 101. They are directed to a patent-ineligible natural phenomenon – *i.e.*, naturally occurring sequences encoding the capsid proteins for the AAV rh.10 variant that were found in a tissue sample of a rhesus monkey. The additional elements recited in the claims add no "inventive concept," but instead, merely place the naturally occurring AAV sequences in a "recombinant nucleic acid molecule" that itself is contained in a "cultured host cell" – features that the named inventors and Plaintiffs' expert all admit were well-known, routine, and conventional long before the '617 patent.

3. Dr. Heeb's damages opinion is unreliable for multiple reasons and should be excluded. Dr. Heeb's use of projected profits for future sales of Sarepta's gene therapy product, SRP-9001, violates the Entire Market Value Rule and is contrary to the requirement that a "reasonable royalty award must be based on the incremental value that the patented invention adds to the end product.'" *CSIRO v. Cisco Sys., Inc.*, 809 F.3d 1295, 1301 (Fed. Cir. 2015). Indeed, Dr. Heeb's reliance on the projected, potential profits from a final product "cannot help but skew the damages horizon for the jury, regardless of the contribution of the patented component to this revenue." *Uniloc USA, Inc. v. Microsoft Corp.*, 632 F.3d 1292, 1320 (Fed. Cir. 2011). Likewise, Dr. Heeb's analysis of certain product development agreements serves to artificially drive up the royalty rate, and any reliance on such agreements without the required showing of comparability should be excluded. *ResQNet.com, Inc. v. Lansa, Inc.*, 594 F.3d 860, 872-73 (Fed. Cir. 2010). Finally, Dr. Heeb's reliance on a weighted combination of three theoretical bargaining

methods that he does not fit to the patented technology or facts of this case also renders his opinion inherently unreliable. *VirnetX, Inc. v. Cisco Sys., Inc.*, 767 F.3d 1308, 1332 (Fed. Cir. 2014).

4. Dr. Leone's opinions regarding Sarepta's knowledge and alleged intent for inducement and contributory infringement should be excluded under *Daubert* and Fed. R. Evid. 702. Dr. Leone proffers opinions based on her personal assessment of what Sarepta "must have" known or intended in light of certain documents and testimony that she has reviewed. Dr. Leone's overview of the evidence is an attempt to usurp the role of the fact finder as to Sarepta's knowledge and alleged intent – issues that are well within the capabilities of the jury to decide.

IV. STATEMENT OF FACTS

The '617 patent issued on January 7, 2020, and expired on November 12, 2022. The earliest asserted priority date for the Asserted Claims is June 5, 2002. Ex. 15 at 9-10.

A. The Asserted Claims

The Asserted Claims generally recite a "cultured host cell" containing a "recombinant nucleic acid molecule" encoding a capsid protein for a naturally occurring variant of AAV – designated "AAV rh.10." Ex. 1 at 437:54-440:31. Claim 1 is reproduced below:

> A cultured host cell containing a recombinant nucleic acid molecule
> encoding an AAV vp1 capsid protein having
> a sequence comprising amino acids 1 to 738 of SEQ ID NO: 81 (AAVrh.10) or
> a sequence at least 95% identical to the full length of amino acids 1 to 738 of SEQ ID NO: 81,
> wherein the recombinant nucleic acid molecule further comprises a heterologous non-AAV sequence.

Id. at 437:55-63. In claim 1, the recombinant nucleic acid molecule encodes (i) the recited amino acid sequence for the vp1 capsid protein of AAV rh.10 or (ii) a sequence that is "at least 95% identical" to the recited amino acid sequence. *Id.* at 57-61. The recombinant nucleic acid molecule also comprises a "heterologous non-AAV sequence." *Id.* at 62-63.

Claims 3 and 5 recite a cultured host cell containing a recombinant acid molecule encoding

(i) the amino acid sequence for the vp2 or vp3 capsid protein of AAV rh.10, or (ii) a sequence that is "at least 95% identical" to the recited amino acid sequence. *Id*. at 437:66-438:59, 438:62-439:2.

Claims 7, 9, 12, and 15 recite a cultured host cell containing a recombinant nucleic acid molecule having the recited nucleic acid sequence encoding (i) the vp1, vp2, or vp3 capsid protein of AAV rh.10, or (ii) a sequence that is "at least 95% identical" to the recited nucleic acid sequence. *Id*. at 439:5-18, 439:21-23, 439:30-32, 440:7-9. Claim 7 is reproduced below:

> A cultured host cell containing a recombinant nucleic acid molecule comprising
> (a) nucleotides 845 to 3058 of SEQ ID NO: 59 or a sequence at least 95% identical to nucleotides 845 to 3058 of SEQ ID NO: 59;
> (b) nucleotides 1256 to 3058 of SEQ ID NO: 59 or a sequence at least 95% identical to nucleotides 1256 to 3058 of SEQ ID NO: 59; or
> (c) nucleotides 1454 to 3058 of SEQ ID NO: 59 or a sequence at least 95% identical to nucleotides 1454 to 3058 of SEQ ID NO: 59,
> wherein the recombinant nucleic acid molecule further comprises a heterologous non-AAV sequence.

Claims 2, 4, 6, 8, and 18-25 are dependent claims that recite additional features of the recombinant nucleic acid molecule in the cultured host cell. In claims 2, 4, 6 and 8, the recombinant nucleic acid molecule also comprises a functional rep gene. *Id*. at 437:64-65, 438:60-61, 439:3-4, 439:19-20. In claims 18-21, the rep gene is from AAV2. *Id*. at 440:15-22. In claims 22-25, the recombinant nucleic acid molecule is in the form of a plasmid. *Id*. at 440:23-31.

B. Sarepta's AAV rh.74 Sequences

The sequences that Sarepta uses in its cultured host cells are naturally occurring amino acid and nucleic acid sequences for a different AAV variant – designated "AAV rh.74." Ex. 17 at SRPT0083178. The rh.74 variant was first discovered by researchers at Nationwide Children's Hospital. Ex. 16 at 13:28-14:8 (Example 1); *see also* Ex. 12 at 306:19-307:22, 313:11-314:3.

The AAV rh.74 variant is not disclosed in the '617 patent. Ex. 1 at 11:50-51, 11:53-12:43 (Table 1); Ex. 11 at 277:3-279:6, 280:3-6. The named inventors of the '617 patent admit that they were not the first to isolate AAV rh.74. *See, e.g.*, Ex. 12 at 314:23-315:3, 318:1-5, 333:5-8.

V. LEGAL STANDARDS

Summary judgment is appropriate when "there is no genuine dispute as to any material fact," and "the movant is entitled to judgment as a matter of law." Fed. R. Civ. P. 56(a). Summary judgment may be granted "against a party who fails to make a showing sufficient to establish the existence of an element essential to that party's case, and on which that party will bear the burden of proof at trial." *Celotex Corp. v. Catrett*, 477 U.S. 317, 322 (1986).

Under Federal Rule of Evidence 702, the judge acts as "gatekeeper" to ensure that any expert testimony is relevant and reliable. Fed. R. Evid. 702; *Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579, 589 (1993). Rule 702 provides that expert testimony must be "the product of reliable principles and methods" and must "help the trier of fact to understand the evidence or to determine a fact in issue." Fed. R. Evid. 702.

VI. PLAINTIFFS CANNOT MEET THEIR BURDEN ON INFRINGEMENT

Plaintiffs' expert, Dr. Leone, contends that "the 'claims in the '617 patent' require more than just sequences that are 'at least 95% identical' to rh.10." Ex. 5 at ¶ 375. According to Dr. Leone, sequences that are "at least 95% identical" to the recited rh.10 sequences must also meet several additional criteria in order to fall within the scope of the Asserted Claims. *Id.* at ¶ 405.

Dr. Leone applied these criteria in her analysis of written description and enablement to avoid invalidity. However, she did not include these criteria in her analysis of infringement. Specifically, Dr. Leone has offered no opinion that the sequences in Sarepta's accused cultured host cells satisfy the criteria that she used to interpret the Asserted Claims for purposes of validity. Moreover, the analysis of Sarepta's expert, Dr. Kay, demonstrates that Sarepta's sequences do not meet any of Dr. Leone's additional criteria, and therefore, the accused cultured host cells do not infringe the Asserted Claims. Dr. Kay's non-infringement opinions are unrebutted.

"Because the claims of a patent measure the invention at issue, the claims must be

interpreted and given the same meaning for purposes of both validity and infringement analyses." *Amazon.com*, 239 F.3d at 1351. Applying this bedrock principle, courts have entered judgment of no infringement when patentees have made infringement arguments that contradict their arguments on validity. *See, e.g.*, *CommScope Techs. LLC v. Dali Wireless Inc.*, 10 F.4th 1289, 1298–300 (Fed. Cir. 2021); *Data Engine Techs. LLC v. Google LLC*, 10 F.4th 1375, 1381 (Fed. Cir. 2021).

Here, Dr. Leone applies certain criteria to limit the sequences that fall within the Asserted Claims for purposes of her opinions on written description and enablement. Those criteria must also be satisfied for purposes of proving infringement, which Dr. Leone has failed to do in her analysis of Sarepta's sequences. Without expert testimony on alleged infringement using Dr. Leone's own validity criteria, Plaintiffs cannot meet their burden on infringement. This is particularly so in this case, where the only expert testimony applying Dr. Leone's criteria – from Sarepta's expert, Dr. Kay – demonstrates that Sarepta's sequences do not infringe. Thus, summary judgment of no infringement should be granted as to all Asserted Claims.

A. Dr. Kay Calculated the Number of Sequences that Are "At Least 95% Identical" to the Sequences Recited in the Asserted Claims

In his opening report on invalidity, Sarepta's expert, Dr. Kay, calculated the number of sequences that are "at least 95% identical" to the sequences recited in each of the Asserted Claims in the '617 patent. For example, claim 1 recites a "sequence comprising amino acids 1 to 738 of SEQ ID NO: 81." Ex. 6 at ¶ 201. Sequences that are "at least 95% identical" to the recited sequence in claim 1 may have up to 37 substitutions at any of the 738 positions in the amino acid sequence. *Id.* at ¶ 202. There are 20 naturally occurring amino acids, so each of the modified positions may be substituted with any one of 19 different amino acids. *Id.* at ¶ 222. In total, Dr. Kay calculated that there are 7.8×10^{109} substituted sequences that are "at least 95% identical" to the recited rh.10 amino acid sequence in claim 1. *Id.* at ¶ 281.

Dr. Kay performed similar calculations for each of the Asserted Claims. He calculated the

number of sequences that are "at least 95% identical" to the recited vp2 and vp3 amino acid sequences in claims 3 and 5, and determined that there are 9.7 x 10^{88} and 2.1 x 10^{77} sequences encompassed by each of those claims, respectively. *Id.* Similarly, for claims 7, 9, 12, and 15, Dr. Kay calculated that there are at least 7.8 x 10^{174} nucleic acid molecules that are "at least 95% identical" to the recited sequences. *Id.* Dr. Kay concluded that the limited disclosure in the '617 patent fails to describe or enable the full scope of the "incomprehensibly large" number of sequences that are encompassed by each of the Asserted Claims. *See id.* at ¶¶ 286, 331, 333.

B. In Her Analysis of Validity, Dr. Leone Applied Additional Criteria that Further Limit the Sequences Falling Within the Asserted Claims

In her rebuttal report, Dr. Leone criticizes Dr. Kay's calculations of the number of sequences falling within the "at least 95% identical" element of the Asserted Claims as allegedly "inconsistent with how a person of ordinary skill in the art would have viewed the '617 patent." Ex. 5 at ¶ 309. In particular, Dr. Leone contends that the '617 patent does not guide a POSA to make "random changes" to the sequences in the Asserted Claims. *Id.* at ¶ 310. Instead, according to Dr. Leone, a POSA would understand from the '617 patent that there are specific locations in the recited sequences where changes should and should not be made, and for those locations that may be changed, what those changes should be. *Id.* at ¶¶ 310, 311, 313. Thus, according to Dr. Leone, the Asserted Claims do not encompass all sequences that are "at least 95% identical" to the recited sequences, as Dr. Kay calculated. *Id.* at ¶¶ 309-310. Instead, sequences that are "at least 95% identical" must also meet additional, specified criteria in order to fall within the scope of the "at least 95% identical" element of the Asserted Claims. *Id.* at ¶¶ 310, 311, 313.

According to Dr. Leone, a two-step analysis is required. First, the modified sequence is aligned with the recited rh.10 sequence, and the percent identity is determined. *Id.* at ¶ 405. Second, "[i]f the percent identity [is] greater than 95%," then "the amino acid substitutions different from AAV rh10" must be evaluated. *Id.* In particular, according to Dr. Leone, a POSA

would "(i) assess the location of each substitution to determine if it was in a conserved region or a hypervariable region, (ii) identify whether each substitution was conservative or not, and (iii) compare the substitution against other substitutions in sequences that were known to result in a capsid protein, if expressed, namely those shown in Figure 2 of the '617 patent." *Id.*

In her rebuttal report, Dr. Leone applies these criteria to narrow the scope of the Asserted Claims and argue that they are not invalid for lack of written description and enablement. These criteria are summarized below, with citations where Dr. Leone discusses them to rebut invalidity.

- Substitutions should be "concentrated" in variable regions and "avoided" in conserved regions, as defined by the alignment of amino acid sequences in Figure 2 of the '617 patent. Ex. 5 at ¶¶ 313-318.
- Only "conservative" amino acid substitutions should be made. *Id.* at ¶¶ 319-321.
- Only "relatively few" amino acid substitutions should be made to the recited rh.10 sequences. *Id.* at ¶¶ 337, 343, 382, 384.
- The substitutions must be "rational and reasonable" in light of available sequence alignments, such as Figures 1 and 2 of the '617 patent. *Id.* at ¶ 344.
- A POSA must be able to determine with a "reasonable degree of probability" whether a particular sequence that is "at least 95% identical" to the claimed sequences, if expressed, would result in a protein that "may be used to form an AAV capsid." *Id.* at ¶¶ 323, 334, 406.

Dr. Leone applied these criteria in her analysis of validity to argue that the number of sequences that fall within the Asserted Claims is smaller the values Dr. Kay calculated – although she did not attempt to calculate the number of sequences herself. Based on this narrow interpretation of the sequences that fall within the "at least 95% identical" element, Dr. Leone concluded that the Asserted Claims are not invalid for lack of written description and enablement. *Id.* at ¶¶ 387, 436.

C. Dr. Leone Failed to Apply Her Own Criteria in the Analysis of Alleged Infringement

However, Dr. Leone did not follow her own two-step analysis – which she used to avoid invalidity – to evaluate alleged infringement. For Sarepta's sequences, Dr. Leone relies on the

alignments and percent identity calculations performed by Dr. Metzker. Ex. 4 at ¶¶ 98, 129, 159, 190, 220, 235, 250. On that basis, Dr. Leone concludes that the percent identity of Sarepta's sequences is greater than 95%. *Id.* at ¶¶ 99, 130, 160, 191, 194, 197, 221, 236, 251.

But that is only half the analysis. According to Dr. Leone, even if the percent identity for a particular sequence is greater than 95%, the specific substitutions must then be evaluated to determine whether they meet the additional criteria that Dr. Leone says are required for a particular sequence to fall within the Asserted Claims. Dr. Leone relies on these criteria to limit the number of sequences and narrow the overall scope of the Asserted Claims for written description and enablement. However, she does not apply the same criteria to her analysis of alleged infringement.

In particular, Dr. Leone never evaluates the differences in Sarepta's sequences to determine whether they meet any of her additional criteria. *See id.* at ¶¶ 95-101, 126-132, 156-162, 187-199, 217-223, 232-238, 247-253. For example, in her analysis of claim 1, Dr. Leone does not discuss any of the [redacted] between the vp1 capsid protein sequence for rh.10 and the vp1 capsid protein sequence for rh.74 used in Sarepta's accused cultured host cells. *Id.* at ¶¶ 95-101. Likewise, Dr. Metzker proffers no analysis of the differences in Sarepta's sequences, and provides no opinion as to whether any additional criteria are met. Ex. 8 at ¶¶ 76-84; Ex. 9 at ¶¶ 16, 18, 20.

Without that analysis, Plaintiffs have a failure of proof on infringement. Plaintiffs have proffered insufficient evidence to meet their burden that the sequences in Sarepta's accused cultured host cells satisfy the "at least 95% identical" element, as they have construed that term to include the narrowing criteria that Dr. Leone contends are required to preserve validity. Thus, summary judgment of no infringement should be granted as to all Asserted Claims.

D. It Is Unrebutted that When Dr. Leone's Criteria Are Applied, the Sequences in Sarepta's Accused Cultured Host Cells Do Not Infringe

The only proffered evidence regarding the specific differences in Sarepta's sequences further supports a judgment of no infringement. Sarepta's expert, Dr. Kay, applied the criteria

outlined by Dr. Leone to the sequences in Sarepta's accused cultured host cells. Ex. 7 at ¶¶ 259-309. Dr. Kay concluded that Sarepta's sequences do not satisfy several criteria. *Id*. at ¶ 259. In particular, the substitutions in Sarepta's sequences (1) are not "conservative," as defined by Dr. Leone, (2) are not "relatively few" in number, (3) are not "rational and reasonable," as described in Dr. Leone's rebuttal report, and therefore, (4) a POSA would not be able to determine with a "reasonable degree of probability" whether the modifications in Sarepta's sequences would result in sequences that, if expressed, would be capable of forming a capsid. *Id*. at ¶¶ 262, 291.

The expert opinions of Dr. Kay on non-infringement are wholly unrebutted. Thus, there is no material issue of fact on this issue – for which Plaintiffs bear the burden at trial – and summary judgment of no infringement as to all Asserted Claims should be granted.

VII. THE ASSERTED CLAIMS ARE NOT PATENT ELIGIBLE

The Asserted Claims of the '617 patent are directed to patent-ineligible natural phenomena. *See Alice Corp. Pty. Ltd. v. CLS Bank Intern*., 573 U.S. 208 (2014). It is undisputed that the rh.10 amino acid and nucleic acid sequences recited in the Asserted Claims are naturally occurring, and therefore, unpatentable. *See Ass'n for Molecular Pathology v. Myriad Genetics, Inc*., 569 U.S. 576, 589-94 (2013). It is also undisputed that the additional elements of the Asserted Claims are all well-known features in the prior art that reflect well-understood, routine, and conventional activity engaged in by the scientific community long before the '617 patent. These additional elements add nothing to transform the naturally occurring rh.10 sequences into patent-eligible subject matter. Thus, there is no material issue of fact, and summary judgment should be granted that the Asserted Claims are invalid under 35 U.S.C. § 101. *See Mayo Collaborative Svcs. v. Prometheus Labs., Inc.,* 566 U.S. 66, 76, 80 (2012) (affirming summary judgment).

The Supreme Court has "set forth a [two-step] framework for distinguishing patents that claim laws of nature, natural phenomena, and abstract ideas from those that claim patent-eligible

applications of those concepts." *Alice*, 573 U.S. at 217 (citing *Mayo*, 566 U.S. at 77-78).

First, in step one, the claims at issue are evaluated to determine whether they are "directed to" a patent ineligible concept. *Id.* This step involves an analysis of "the 'focus of the claimed advance over the prior art' to determine if the claim's 'character as a whole' is directed to excluded subject matter." *Intellectual Ventures I LLC v. Erie Indem. Co.*, 850 F.3d 1315, 1325 (Fed. Cir. 2017); *TecSec, Inc. v. Adobe Inc.*, 978 F.3d 1278, 1292-93 (Fed. Cir. 2020); *see also AI Visualize, Inc. v. Nuance Comm's, Inc.*, 610 F. Supp. 3d 638, 645-46 (D. Del. 2022).

The inventors' own description of their "discovery" as a natural phenomenon or law of nature is particularly compelling evidence that the claims are directed to ineligible subject matter. *See, e.g.*, *Roche Molecular Sys. v. Cepheid*, 905 F.3d 1363, 1371-72 (Fed. Cir. 2018); *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371, 1376 (Fed. Cir. 2015).

Second, in step two, the claims are evaluated to determine whether the additional elements add an "inventive concept" to ensure that the patent in practice amounts to "significantly more" than a patent upon the natural law or phenomenon itself. *Mayo*, 566 U.S. at 72-73. In making this assessment, the claim elements should be considered individually and "as an ordered combination" to determine whether the additional elements "transform the nature of the claim" into something patent eligible. *Id.* at 78-80.

However, the "inventive concept" necessary to satisfy the second step cannot be furnished by the unpatentable natural phenomena or law of nature itself. *See, e.g.*, *Athena Diagnostics, Inc. v. Mayo Collaborative Servs., LLC*, 915 F.3d 743, 754 (Fed. Cir. 2019). Concessions that the additional claim elements – other than the natural phenomenon or law of nature itself – were in the prior art are generally conclusive as to patent ineligibility. *See, e.g.*, *CareDX, Inc. v. Natera, Inc.*, 40 F.4th 1371, 1380 (2022); *Genetic Techs. Ltd. v. Merial L.L.C.*, 818 F.3d 1369, 1377 (Fed. Cir. 2016); *Ariosa Diagnostics*, 788 F.3d at 1377.

A. Step 1: The Asserted Claims Are Directed to Patent-Ineligible Subject Matter

The Asserted Claims recite a "cultured host cell" containing a "recombinant nucleic acid molecule" encoding the amino acid or nucleic acid sequence for the capsid protein of the AAV variant – rh.10. The amino acid and nucleic acid sequences for rh.10 are naturally occurring – and therefore, not patent eligible. *Myriad*, 569 U.S. at 589-94. Yet, this unpatentable element in each of the Asserted Claims is exactly what the named inventors identified in the '617 patent as their claimed advance over the prior art – *i.e.*, the isolation of the rh.10 sequence from a naturally occurring source. Thus, at the most fundamental level, the Asserted Claims are directed to a natural phenomenon – the naturally occurring rh.10 sequences – which are not patentable subject matter, and the first step of the two-part test is satisfied.

1. The AAV rh.10 Sequences in the Asserted Claims Are Naturally Occurring

There is no dispute that the rh.10 amino acid and nucleic acid sequences recited in the Asserted Claims are naturally occurring. These sequences are the strings of amino acids and nucleic acids for the vp1, vp2, and vp3 capsid proteins for the rh.10 variant – all of which are found in nature. This is confirmed by the '617 patent itself, the testimony of the named inventors (Dr. Gao, Dr. Wilson, and Mr. Alvira), and the testimony of Plaintiffs' technical expert, Dr. Leone.

- The '617 patent discusses the isolation of naturally occurring AAV sequences and identifies the source of the tissue sample for each variant – including rh.10 – in Table 1. Ex. 1 at 3:24-35, 11:50-51, Table 1.
- At her deposition, Dr. Leone agreed that the nucleic acid sequence encoding the AAV rh.10 capsid protein is naturally occurring. Ex. 10 at 70:12-72:17.
- Dr. Leone also agreed that the amino acid sequence for the rh.10 capsid protein is naturally occurring. *Id.* at 72:22-79:2.
- In her rebuttal report, Dr. Leone relies on the fact that the amino acid sequences in Figure 2 of the '617 patent – including rh.10 – are naturally occurring to support her opinion that the Asserted Claims are not invalid. Ex. 5 at ¶ 322 ("the sequences in Figure 2 correspond to naturally occurring AAV capsid proteins").

- Likewise, all three named inventors confirmed that the rh.10 nucleic acid sequence for the AAV capsid protein was obtained from a naturally occurring source – a tissue sample from a rhesus monkey. Ex. 11 at 53:20-54:13, 63:10-15, 68:6-11, 96:14-24, 99:12-17, 104:3-6, 152:11-153:7, 212:12-214:17; Ex. 12 at 19:11-13, 22:12-15, 69:11-15, 71:11-14, 91:19-92:9, 93:2-94:2; Ex. 13 at 115:4-118:2.

- In fact, as Mr. Alvira testified, optimization and validation experiments were performed to ensure that the nucleic acid sequences they obtained for the AAV variants were not artifacts of the PCR method but were the actual, naturally occurring sequences in the tissues. Ex. 13 at 93:8-94:14, 96:9-100:23.

- Dr. Gao and his colleagues deduced the amino acid sequence encoding the vp1 capsid protein for rh.10 from the naturally occurring nucleic acid sequence. Ex. 11 at 97:2-9, 99:19-101:10, 104:21-105:17; Ex. 12 at 69:16-19, 72:18-74:2.

- Dr. Wilson and his colleagues determined that the isolated sequences came from infection with a naturally occurring AAV virus having AAV capsid proteins with the deduced amino acid sequence. Ex. 12 at 20:9-22:11; Ex. 13 at 99:24-100:23.

Under the Supreme Court's decision in *Myriad*, the naturally occurring amino acid and nucleic acid sequences for rh.10 are not patent-eligible subject matter. *See Myriad*, 569 U.S. at 589-94. Like the unpatentable DNA sequences in *Myriad*, the "location and order" of the amino acids and nucleic acids in the AAV rh.10 sequences recited in the Asserted Claims "existed in nature" before the named inventors found them. *See id.* at 590. Likewise, isolating the sequences encoding the AAV rh.10 capsid proteins "from [the] surrounding genetic material [in a naturally occurring tissue sample] is not an act of invention." *See id.* at 591.

The language of the Asserted Claims highlights the naturally occurring rh.10 sequences as the central element in each Asserted Claim. The naturally occurring sequences are the only elements identified with any degree of specificity – *i.e.*, by reference to the specific string of amino acids and nucleic acids set forth in SEQ ID NO: 81 and SEQ ID NO: 59, respectively. *See, e.g.*, Ex. 1 at 437:55-63 (claim 1), 439:5-18 (claim 7).

For example, the central element of claim 1 is the amino acid sequence for the vp1 capsid protein for AAV rh.10. The named inventors isolated the nucleic acid sequence encoding the amino acids for the vp1 capsid protein for rh.10 in a tissue sample taken from a rhesus monkey.

Ex. 1 at 9:8-17, 11:50-12:42 (Table 1), 38:2-7. The recited amino acid sequence for the vp1 capsid of rh.10 – *i.e.*, amino acids 1 to 738 of SEQ ID NO: 81 – is a naturally-occurring sequence that the inventors deduced from the isolated nucleic acid sequence. Ex. 11 at 104:21-105:17; Ex. 12 at 69:16-19. The recited amino acid sequence is exactly the sequence of the vp1 capsid protein for rh.10 that is found in nature. Ex. 10 at 77:24-79:2; Ex. 5 at ¶ 322.

Like claim 1, the central element of claim 7 is a naturally-occurring sequence – in this case, the sequence of nucleotides identified in the specification at SEQ ID NO: 59. The portions of the nucleotide sequence recited in elements (a), (b), and (c) encode the vp1, vp2, and vp3 capsid proteins for the naturally-occurring rh.10 variant. Ex. 4 at ¶ 63; Ex. 10 at 66:11-70:11; *see also* Ex. 6 at ¶¶ 134-137. This sequence was extracted from a tissue sample taken from a rhesus monkey. Ex. 1 at 9:8-17, 11:53-12:42 (Table 1); Ex. 11 at 53:20-54:13; Ex. 12 at 69:11-15; Ex. 13 at 115:4-117:22. And like the amino acid sequence, the recited nucleotide sequence encoding the rh.10 capsid proteins is exactly the same sequence found in nature. Ex. 10 at 70:12-71:5.

The remaining elements in the Asserted Claims do not have the same specificity as the elements directed to the naturally occurring AAV rh.10 sequences. The additional elements place the naturally occurring sequences in a generic "recombinant nucleic acid molecule" that is unspecified and includes additional, "heterologous non-AAV sequences," which are also unspecified. *See, e.g.*, Ex. 1 at 437:55-56, 62-63 (claim 1), 439:5-18 (claim 7). The nucleic acid molecule can be a "plasmid" or in any other form. *Compare id.* at 437:55-56 (claim 1), *and* 439:5-6 (claim 7), *with* 440:23-31 (claims 22-25). The nucleic acid molecule can also include other, known AAV sequences, such as an "AAV2 rep gene." *Id.* at 440:16-23 (claims 18-21). Finally, the recombinant nucleic acid molecule is inserted into "a cultured host cell," which is again generic and unspecified. *Id.* at 437:55 (claim 1), 439:5 (claim 7). These additional elements do not include any further details. Instead, they appear to be drafted in the broadest possible terms, without

identification of any purported advancement or contribution to the art.

2. The '617 Patent Touts the Naturally Occurring Sequences as the Alleged Contribution over the Prior Art

In the '617 patent, the named inventors identify the claimed advance over the prior art as the isolation of the naturally occurring rh.10 sequences. This is the only alleged contribution that is recited in the Asserted Claims. Thus, the description of the alleged invention in the specification shows that the character of the Asserted Claims as a whole is directed to patent-ineligible subject matter. *See, e.g.*, *Roche*, 905 F.3d at 1371-72; *Ariosa Diagnostics*, 788 F.3d at 1376.

The '617 patent discloses a method for detecting and isolating naturally occurring AAV sequences in mixed DNA samples extracted from human and non-human primate tissues. Ex. 1 at 1:57-66. The disclosed method uses the polymerase chain reaction ("PCR") to amplify a variable region of DNA encoding the AAV capsid protein that is flanked by constant regions – designated by the applicants as the "signature region." *Id.* at 3:24-35, 35:19-26; 35:41-36:3. Amplification of the "signature region" in a mixed DNA sample indicates the presence of naturally occurring AAV nucleic acid sequences. *Id.* at 36:5-11.

The named inventors used the "signature region" PCR method to identify sequences for naturally occurring AAV variants – such as rh.10. They performed an initial analysis of tissue samples from non-human primates, including rhesus monkeys, cynomologous macaques, chimpanzees, and baboons for strains of AAV. *Id.* at 35:19-26; 35:30-33; 36:16-28; 39:7-10. They also performed a more extensive analysis of AAV distribution in tissue samples from rhesus monkeys. *Id.* at 35:36-39; 39:10-13. They found AAV sequences "throughout a wide array" of different tissues. *Id.* at 35:39-40, 39:14-15. Altogether, the named inventors isolated 50 AAV sequences from non-human primates. *Id.* at 38:2-3; 40:6-9.

The naturally occurring AAV sequences, including rh.10, are listed in Table 1. *Id.* at 11:50-51, Table 1. The sequences are numbered in order as they were isolated, with a prefix indicating

the species of non-human primate from which they were derived – *i.e.*, rh.10 is the tenth AAV isolated from rhesus monkey. *Id.* at 40:9-12, Table 1. Alignments of the nucleic acid and amino acid sequences are shown in Figures 1 and 2, respectively. *Id.* at 2:25-3:15, Figures 1-2.

In the '617 patent, the named inventors tout the identification of these naturally occurring AAV sequences as their contribution to the art. They refer to the naturally occurring variants as "novel AAV serotypes." *Id.* at 1:55-2:18, 2:25-3:15, 3:36-44, 11:17-51. And they devote the vast majority of the specification to a discussion of these allegedly "novel" AAV variants – including rh.10. However, the AAV sequences encoding the vp1, vp2, and vp3 capsid proteins for rh.10 – and identified as "novel" in the '617 patent – are naturally occurring sequences, which are not patentable. There is no other element of the Asserted Claims that is identified in the specification as an allegedly inventive contribution. Thus, the named inventors' own characterization of their alleged contribution to the art – the identification of naturally occurring rh.10 sequences – demonstrates that the Asserted Claims are directed to excluded subject matter.

This is confirmed by the deposition testimony of Dr. Guangping Gao – a named inventor and the University of Pennsylvania's designee on the topics of conception and reduction to practice of the Asserted Claims and the research and development of the subject matter of the '617 patent. Ex. 11 at 34:15-35:23. Dr. Gao testified that the rh.10 sequences are the feature of the Asserted Claims that distinguish them from the prior art. *Id.* at 106:23-107:13. As Dr. Gao explained, "[t]he value here is rhesus 10 sequence." *Id.* at 105:19-106:12.

Similarly, Dr. Leone identified the naturally occurring rh.10 sequences as the "invention" of the Asserted Claims. Ex. 10 at 104:19-105:2 ("Q. Okay. Was making a recombinant nucleic acid molecule an invention of the named inventors? A. The invention was discovering this specific sequence of AAVrh.10. . . ."), 105:5-12 ("Q. Was making a recombinant nucleic acid molecule with a functional rep gene the invention of the named inventors? A. So the invention was making

an AAVrh.10, was discovering the sequence and then encode for the AAVrh.10 capsid."). Like the '617 patent, Dr. Gao and Dr. Leone consistently point to the same thing as the allegedly novel feature of the Asserted Claims – *i.e.*, the naturally occurring rh.10 sequences. This testimony confirms that the Asserted Claims are directed to unpatentable natural phenomena.

3. Plaintiffs Seek to Preclude All Uses of the Naturally Occurring AAV rh.10 Sequences in Cultured Host Cells

The Supreme Court has explained the rationale underlying the exceptions to patentability under 35 U.S.C. § 101. *Alice*, 573 U.S. at 216; *see also Myriad*, 569 U.S. at 589:

> We have described the concern that drives this exclusionary principle as one of pre-emption. Laws of nature, natural phenomena, and abstract ideas are the basic tools of scientific and technological work. Monopolization of those tools through the grant of a patent might tend to impede innovation more than it would tend to promote it, thereby thwarting the primary object of the patent laws.

Here, the Asserted Claims purport to cover any use of the naturally occurring rh.10 sequences in a cultured host cell for any research or commercial application. In particular, Plaintiffs seek to preclude all uses of the naturally occurring rh.10 sequences for any purpose related to gene therapy for the treatment of any disease, no matter the therapeutic indication. *See* Ex. 5 at ¶ 81; Ex. 4 at ¶¶ 47-57; Ex. 18 at ¶ 6. Thus, the Asserted Claims are nothing more than a drafting effort designed to monopolize the naturally occurring rh.10 sequences for any purpose relating to gene therapy, thereby inhibiting "future innovation premised upon them" – precisely the outcome that Section 101 is designed to prevent. *See Mayo*, 566 U.S. at 86.

4. Patentability Does Not Depend on the Vagaries of the "Draftsman's Art"

Plaintiffs contend that the Asserted Claims are not "directed to" patent-ineligible subject matter because they recite additional elements, such as a "cultured host cell" containing a "recombinant nucleic acid molecule," which are not found in nature. Ex. 15 at 49-50; Ex. 5 at ¶¶ 70-79, 89. Thus, according to Plaintiffs, the Asserted Claims are necessarily patentable.

However, as the Supreme Court has long cautioned, eligibility under § 101 does not depend simply on the "draftsman's art." *Alice*, 573 U.S. at 226; *Mayo*, 566 U.S. at 72 (citing *Parker v. Flook*, 437 U.S. 584, 593 (1978)). In *Flook*, the Supreme Court explained that "respondent incorrectly assumes that if a process application implements a principle in some specific fashion, it automatically falls within the patentable subject matter of § 101. . . ." *Flook*, 437 U.S. at 593. That "would make the determination of patentable subject matter depend simply on the draftsman's art and would ill serve the principles underlying the prohibition against patents for 'ideas' or phenomena of nature." *Id.*

Similarly, here, the Asserted Claims are not automatically patent eligible subject matter merely because they recite a "cultured host cell" containing a "recombinant nucleic acid molecule." Plaintiffs' argument is akin to saying that an abstract idea is patentable merely because the claims recite a generic "computer" to implement the abstract idea. *See Alice*, 573 U.S. at 221. This Court has rejected similar arguments many times in other cases. *See, e.g.*, *Callwave Comm's, LLC v. AT & T Mobility, LLC*, 207 F. Supp. 3d 405, 413 (2016); *Eagle View Techs., Inc. v. Roofr, Inc.*, C.A. No. 21-1852-RGA, 2023 WL 315633, at *5, 8, 9 (D. Del. Jan. 19, 2023).

Instead, when analyzed under the correct standard for patent eligibility, the focus of the alleged advancement in the Asserted Claims is the naturally occurring rh.10 sequences themselves. The additional elements, such as a generic "cultured host cell" and an unspecified "recombinant nucleic acid molecule," do not change the character of the Asserted Claims as a whole. As such, the Asserted Claims are directed to naturally occurring AAV rh.10 sequences – which are patent-ineligible subject matter, and the first step of the two-part test is satisfied.

B. Step 2: The Additional Elements in the Asserted Claims Add Nothing Inventive to the Naturally Occurring Sequences

There is no dispute that the additional elements of the Asserted Claims were all well-known features in the prior art that reflect well-understood, routine, and conventional activity engaged in

by the scientific community long before the '617 patent. In her rebuttal report, Dr. Leone explains that researchers in the field of gene therapy have been creating recombinant AAV vectors using cultured host cells "since at least the early 1980's." Ex. 5 at ¶ 401. She then summarizes the elements in the Asserted Claims that she concedes would have been well within the knowledge of a POSA. *See* Ex. 5 at ¶¶ 401-404. Dr. Leone concludes that "[a] person of ordinary skill in the art would have had all the tools needed to make and use cultured host cells containing nucleic acids encoding the full scope of the claimed capsid proteins." Ex. 5 at ¶ 404.

As Dr. Leone concedes, the recombinant nucleic acid molecules recited in the Asserted Claims are made up of known elements (*e.g.*, a "heterologous non-AAV sequence," and a "functional AAV2 rep gene") that are prepared using conventional methods and introduced into "a cultured host cell" using well-known techniques. This is confirmed by the '617 patent and prosecution history, and the testimony of the named inventors, as discussed further below.

As the Supreme Court has explained, "simply appending conventional [elements], specified at a high level of generality, to laws of nature, natural phenomena, and abstract ideas cannot make those laws, phenomena, and ideas patentable." *Mayo*, 566 U.S. at 82; *see also Callwave*, 207 F. Supp. 3d at 410. Thus, the additional elements in the Asserted Claims, either alone or in combination, do not transform the naturally occurring rh.10 sequences into patent-eligible subject matter, and the second step of the two-part test is satisfied.

1. The Additional Elements in the Asserted Claims Are Routine and Conventional

None of the additional elements in the Asserted Claims add any "inventive concept" to the recited AAV rh.10 sequences found in nature.

Cultured Host Cells. It is undisputed that the use of cultured host cells was routine in the art, and adds nothing inventive to the naturally occurring rh.10 sequences in the Asserted Claims.

- Dr. Wilson testified that, before the '617 patent, cultured host cells containing

recombinant nucleic acid molecules were an important tool in basic biological research. Ex. 12 at 57:11-58:2.

- Dr. Wilson and his colleagues were not the first to use cells grown in culture. *Id.* at 54:3-55:11. Nor were they the first to make a cultured host cell containing a recombinant nucleic acid molecule. *Id.* at 55:13-56:9, 56:21-57:10.

- As Dr. Wilson explained during prosecution of a related application, "[p]ackaging host cells for producing AAV were known to those of ordinary skill in the art at the time this invention was made. Also known were a variety of methods for generating such packaging host cells." Ex. 14 at ¶ 5(b); *see also* Ex. 5 at ¶ 402.

- In the same declaration, Dr. Wilson also explained that "[m]ethods of generating recombinant adeno-associated viruses in packaging host cells were well known as of November 2001." Ex. 14 at ¶ 3(d); *see also id.* at ¶ 3(e); Ex. 5 at ¶ 402.

- At his deposition, Dr. Wilson confirmed that he and his colleagues were not the first to use cultured host cells to make recombinant AAVs. Ex. 12 at 31:1-14. As of 2001, cultured host cells for making recombinant AAVs were known in the art. *Id.* at 166:11-167:3, 167:14-168:5, 178:24-179:20. And methods for making recombinant AAVs using cultured host cells were well known before the '617 patent. *Id.* at 34:13-21, 168:6-23, 170:17-171:13; *see also* Ex. 5 at ¶¶ 401, 402.

- Similarly, Dr. Gao testified that cultured host cells had been used in the art to make recombinant AAVs before the '617 patent. Ex. 11 at 48:22-49:9, 68:12-69:2; 74:9-11, 343:23-347:12, 347:20-350:22. Methods were known in the art for making recombinant AAVs using cultured host cells – such as triple transfection methods and the use of genetically modified host cells. *Id.* at 74:23-75:2, 343:23-347:12, 347:20-350:22; *see also* Ex. 5 at ¶ 401.

Recombinant Nucleic Acid Molecules. Likewise, it is undisputed that nothing about the recombinant nucleic acid molecules recited in the Asserted Claims is inventive.

- Dr. Leone explains that "[o]rdinary molecular biology methods would, as a matter of routine, involve making recombinant nucleic acid molecules." Ex. 5 at ¶ 401.

- As Dr. Gao and Dr. Wilson testified, methods for combining nucleic acid molecules from different sources to make a recombinant nucleic acid molecule were known in the art. Ex. 11 at 77:8-78:3, 350:23-352:7, 352:9-354:12; Ex. 12 at 39:3-14, 50:14-51:1, 63:21-66:9.

- Likewise, the specification of the '617 patent describes the "assembly of selected DNA sequences" as requiring only "conventional" techniques that were "well known" in the art. Ex. 1 at 25:37-47; *see also* Ex. 5 at ¶ 403.

- Dr. Gao and Dr. Wilson both confirmed that they were not the first to make a cultured host cell containing a recombinant nucleic acid molecule encoding an

AAV capsid protein. Ex. 11 at 76:1-5, 107:15-21, 109:10-17; Ex. 12 at 36:9-16.

- Before the '617 patent, nucleic acid molecules encoding AAV capsid proteins were known. Ex. 11 at 76:23-77:6; Ex. 12 at 36:24-37:4.
- And methods for introducing recombinant nucleic acids into cultured host cells – such as transfection and transduction – were known. Ex. 11 at 78:14-79:4, 354:13-356:15; Ex. 12 at 39:15-23, 59:14-60:8.
- In fact, the '617 patent directs a POSA to use known methods to obtain cultured host cells containing a recombinant nucleic acid molecule, as recited in the Asserted Claims. Ex. 1 at 25:48-51; *see also id.* at 17:26-29, 18:52-57, 22:34-43.

"At Least 95% Identical" to Naturally Occurring AAV rh.10 Sequences. It is undisputed that the element "at least 95% identical" adds nothing inventive to the Asserted Claims.

- As both Dr. Gao and Dr. Wilson testified, [redacted] Ex. 11 at 176:2-177:13, 177:21-178:4; Ex. 12 at 78:23-79:23, 439:22-440:16, 441:18-442:2.
- In particular, [redacted] Ex. 12 at 442:3-443:9; Ex. 11 at 185:7-186:11.
- [redacted] Ex. 11 at 189:14-16.

Moreover, it is undisputed that routine techniques were available before the '617 patent to create modified sequences that are "at least 95% identical" to the naturally occurring rh.10 sequences recited in the Asserted Claims.

- Dr. Leone concedes that "it would have been a routine matter for a person of ordinary skill to make modifications to the naturally occurring nucleic acid sequence encoding the AAV rh.10 capsid protein." Ex. 5 at ¶ 401.
- As Dr. Leone explains, "[o]nce a person of ordinary skill in the art obtained the claimed, previously unknown, sequences taught in the '617 patent, they would have known how to make and use variations of the sequences that are 95% identical to the claimed sequences." *Id.* at ¶ 401, n.7.
- Similarly the specification of the '617 patent explains that methods for modifying nucleic acid sequences were conventional and well known to those skilled in the art at the time of the '617 patent. Ex. 1 at 17:20-35; Ex. 5 at ¶¶ 401, 403.
- For example, techniques for site directed mutagenesis were well known in the art as of the priority date. Ex. 1 at 13:44-46; Ex. 5 at ¶ 401.

Heterologous Non-AAV Sequences. It is undisputed that the element "heterologous non-AAV sequence" does not add anything beyond what was already conventional and routine.

- As Dr. Wilson testified, he and his colleagues did not invent "new" heterologous non-AAV sequences. Ex. 12 at 52:1-24, 53:16-54:1.
- Dr. Gao and Dr. Wilson were not the first to combine an AAV sequence encoding a capsid protein and a heterologous non-AAV sequence into a single recombinant nucleic acid molecule. *Id.* at 61:5-62:1, 63:14-20.
- Likewise, Dr. Gao and Dr. Wilson were not the first to make a cultured host cell containing a recombinant nucleic acid molecule encoding an AAV capsid protein and a heterologous non-AAV sequence. Ex. 11 at 93:21-94:5, 95:12-19.

Functional Rep Genes. It is undisputed that the dependent claims directed to "functional rep genes" are similarly directed to well-known, routine, and conventional subject matter.

- As Dr. Wilson testified, he and his colleagues were not the first to do experiments in which a rep gene was introduced into a cultured host cell. Ex. 12 at 85:17-86:7, 86:18-87:15; *see also* Ex. 11 at 102:19-103:4.
- Cultured host cells containing a functional rep gene were used to make recombinant AAVs before the '617 patent. Ex. 12 at 87:17-88:8, 88:17-22; Ex. 11 at 103:16-22.
- Additionally, Dr. Gao and Dr. Wilson both testified that the AAV2 rep gene was known before the '617 patent. Ex. 11 at 55:12-56:7, 79:23-80:3, 119:11-23; Ex. 12 at 102:14-18, 103:8-104:13.
- They were not the first to make a cultured host cell containing a recombinant nucleic acid molecule encoding an AAV2 rep gene. Ex. 11 at 80:19-81:1; Ex. 12 at 102:20-103:6, 104:14-105:4.
- Cultured host cells containing a functional rep gene from AAV2 had been used to make recombinant AAVs prior to the '617 patent. Ex. 12 at 105:6-10.

Plasmids. It is undisputed that nucleic acid molecules in the form of a "plasmid" were well-known in the art for delivery of sequences to cultured host cells.

- The '617 patent discusses the use of plasmids and other vectors to deliver nucleic acid molecules to host cells as involving nothing more than conventional techniques. Ex. 1 at 17:20-35; *see also* Ex. 5 at ¶ 403.
- Dr. Gao and Dr. Wilson both confirmed that nucleic acid molecules in the form of a plasmid were known in the art. Ex. 11 at 80:5-10; Ex. 12 at 39:24-40:4, 40:17-21, 105:15-106:4.

- As they both testified, they were not the first to make a cultured host cell containing a recombinant nucleic acid molecule in the form of a plasmid. Ex. 11 at 80:12-17, 120:13-121:12, 122:10-17; Ex. 12 at 41:20-42:5, 106:5-9, 107:8-11.

- Plasmids had been used to introduce nucleic acid sequences into cultured host cells long before the '617 patent. Ex. 11 at 121:14-20; Ex. 12 at 40:22-41:1, 106:11-15.

- More than that, plasmids had been used in cultured host cells to make recombinant AAVs prior to the '617 patent. Ex. 12 at 108:3-109:2.

2. The Combination of Routine and Conventional Elements in the Asserted Claims Is Not Patent Eligible

It is undisputed that the combination of elements does not add an "inventive concept" that amounts to "significantly more" than the naturally occurring rh.10 sequences themselves.

- Dr. Leone concedes that "conventional genetic engineering and recombinant engineering techniques were available to prepare cultured host cells containing a nucleic acid molecule encoding an AAV capsid protein." Ex. 5 at ¶ 401.

- As Dr. Leone explains, "[a] person of ordinary skill in the art as of the priority date would have been very familiar with the use of cultured host cells to produce viruses from recombinant vectors and would have viewed those techniques as routine." *Id.*

The '617 patent confirms that the combination of elements is not "inventive."

- The specification explains that "[t]he methods used to construct any embodiment of this invention are known to those with skill in nucleic acid manipulation and include genetic engineering, recombinant engineering, and synthetic techniques." Ex. 1 at 18:57-61; *see also* Ex. 5 at ¶ 403.

- "The methods employed for constructing embodiments of this invention are conventional genetic engineering or recombinant engineering techniques such as those described in the references above." Ex. 1 at 24:3-6; *see also* Ex. 5 at ¶ 403.

- Similarly, according to the specification, "methods of generating [recombinant] AAV virions are well known and the selection of a suitable method is not a limitation on the present invention." Ex. 1 at 18:63-65.

3. Plaintiffs Cannot Rely on the Patent-Ineligible AAV rh.10 Sequences as the Alleged Inventive Contribution

It is well established that the "inventive concept" necessary for the second step cannot be furnished by the unpatentable natural phenomena itself. *See, e.g., Genetic Techs.*, 818 F.3d at 1376. As the Federal Circuit has explained:

> The inventive concept necessary at step two of the *Mayo/Alice* analysis cannot be furnished by the unpatentable law of nature (or natural phenomenon or abstract idea) itself. That is, under the *Mayo/Alice* framework, a claim directed to a newly discovered law of nature (or natural phenomenon or abstract idea) cannot rely on the novelty of that discovery for the inventive concept necessary for patent eligibility; instead, the application must provide something inventive, beyond mere "well-understood, routine, conventional activity."

Id. (citing *Mayo,* 566 U.S. at 72, *Myriad,* 569 U.S. at 591; *Ariosa Diagnostics,* 788 F.3d at 1379).

Here, the Asserted Claims are directed to a "cultured host cell" containing a "recombinant nucleic acid molecule" encoding a naturally occurring AAV capsid protein sequence and a "heterologous non-AAV sequence" – a combination that was known long before the '617 patent and could be prepared using well-known, routine, and conventional techniques. As Plaintiffs' witnesses concede, the additional elements recited in the Asserted Claims do not provide an "inventive concept" that amounts to "significantly more" than the naturally occurring rh.10 sequences themselves, and therefore, the second step of the two-part test is satisfied.

VIII. DR. HEEB'S DAMAGES OPINIONS SHOULD BE EXCLUDED

Throughout this litigation, Plaintiffs have asserted that this case is not about Sarepta's gene-therapy products in development. *See, e.g.,* D.I. 20 at 5 ("The claims are not directed to a potential gene therapy treatment."); *id.* at 8 (The "cultured host cells, not SRP-9001, are accused of infringement…"); *see also* Ex. 19 at 49:9-10 ("[T]he claims at issue today are about the cultured host cell."); 54:21-23 ("These cultured host cells simply have nucleic acid that encode the vp1. They're not the final gene therapy product."). Rather, the accused technology is limited to cultured host cells containing recombinant nucleic acid molecules that encode AAV capsid proteins for the naturally occurring AAVrh.10 capsid, or sequences that are at least 95% identical to the specified AAVrh.10 sequences. *Id.; see also* Ex. 4 at ¶ 65.

Even though Sarepta's gene-therapy products are not accused, Plaintiffs' damages expert, Dr. Heeb, uses Sarepta's forecasts for future sales of SRP-9001, a final gene therapy product used

to treat Duchenne muscular dystrophy ("DMD"), as the base for his royalty opinion. *See, e.g.,* Ex. 20 at ¶¶ 8, 18-19. When the '617 patent expired on November 12, 2022, SRP-9001 was not yet approved by the FDA, and no sales had yet been made.[1] Yet Dr. Heeb contends that, at the time of the hypothetical negotiation in January of 2020, Sarepta would have agreed to a staggering up front, lump sum royalty of [redacted].[2] Ex. 21 at ¶ 22. Dr. Heeb's opinion is fundamentally flawed. Dr. Heeb begins with Sarepta's projected profits for SRP-9001, without any attempt to determine the patented technology's contribution to SRP-9001. Dr. Heeb compounds his error by relying on non-comparable agreements as purported "corroboration" of the inflated royalty he derived from Sarepta's forecasts for SRP-9001. Further, Dr. Heeb's methodology relies on a weighted combination of theoretical bargaining methods that are unconnected to the value of the patented technology and the facts of this case. For all of these reasons, Dr. Heeb's unreliable, inflated opinion concerning the reasonable royalty for Sarepta's alleged use of the accused cultured host cells should be excluded.

For opinions on damages, "'[t]he essential requirement' for reliability under *Daubert* 'is that the ultimate reasonable royalty award must be based on the incremental value that the patented invention adds to the end product.'" *CSIRO*, 809 F.3d at 1301. Dr. Heeb makes no attempt to "tie proof of damages to the claimed invention's footprint in the market place" – the central guiding principle that the Federal Circuit has held must be the ultimate guidepost for any reasonable royalty analysis. *ResQNet*, 594 F.3d at 869. By failing to adhere to the fundamental principles required

[1] On June 22, 2023, more than seven months after the '617 patent expired, the FDA approved SRP-9001, tradename ELEVIDYS™, for the treatment of ambulatory pediatric patients aged 4 through 5 years with DMD with a confirmed mutation of the DMD gene. Ex. 27 at 1.

[2] In his May 2, 2023 Corrected Expert Report, Dr. Heeb opined that the up front, lump sum royalty should be [redacted], and that Sarepta's "maximum willingness to pay" or "MWP" was [redacted]. Ex. 20 at ¶¶ 14, 18, 174. In his June 23, 2023 reply report, Dr. Heeb revised those opinions to a lump sum royalty of [redacted] and an MWP of [redacted]. Ex. 21 at ¶¶ 22-23.

by the Federal Circuit for the determination of a reasonable royalty, Dr. Heeb's damages analysis is unreliable and should be precluded at trial.

A. Dr. Heeb Failed to Apportion the Applicable Royalty Base and Improperly Relied on Projected Profits that Necessarily Skew the Damages Horizon

Dr. Heeb's opinion "is based on a forecast of the value of the license to each party of avoiding a patent-related 35 month delay" in the launch of SRP-9001. Ex. 20 at ¶ 15. Dr. Heeb relies on Sarepta's forecasts of revenues and profits for SRP-9001, then calculates Sarepta's projected profits both with and without the hypothetical license to arrive at his opinion that the value to Sarepta of the 35 months is approximately [redacted]. Ex. 20 at ¶¶ 18-19; Ex. 21 at ¶ 22. According to Dr. Heeb, the [redacted] accrues "entirely to avoiding the delay from a pause in product development" and "entirely to the '617 patent in isolation." Ex. 20 at ¶¶ 18-19. Dr. Heeb contends that "no further apportionment is necessary" because the entire value of the delay – the difference in net present value of projected profits for SRP-9001 in Dr. Heeb's "license" and "no license" scenarios – is attributable to the '617 patent. *Id.* Under Dr. Heeb's theory, any patentee could rely on the entire profit for a complicated product as a royalty base, no matter how small the contribution of the asserted patent to the overall product, as long as rights to the patent were the last piece necessary to continue product development. As Dr. Heeb asserts, "the hypothetical license to the '617 Patent convey[s] technology that, when added to the technology already possessed by the licensee, gives the licensee the capability to make a product worth [redacted] more than the licensee could achieve without the license.'" Ex. 21 at ¶ 48.

Dr. Heeb's reliance on the total projected profits for SRP-9001 violates the Entire Market Value Rule. For the Entire Market Value Rule to apply, the patentee must show that "the patented feature drives the demand for an entire multi-component product." *LaserDynamics, Inc. v. Quanta Computer, Inc.*, 694 F.3d 51, 67 (Fed. Cir. 2012); *Lucent Techs., Inc. v. Gateway Inc.*, 580 F.3d 1301, 1323-24 (Fed. Cir. 2009). Plaintiffs have never asserted that alleged infringement of the

'617 patent during manufacturing of SRP-9001 drives demand for the SRP-9001 final product. In fact, Plaintiffs' expert on issues related to FDA approval compared the use of the accused cultured host cells to [redacted] used during manufacture. Ex. 22 at ¶ 58. Further, SRP-9001 itself is not accused of infringing the '617 patent. *See, e.g.,* D.I. 20 at 5, 8. And, Plaintiffs do not dispute that critical elements of SRP-9001 – such as the transgene, which actually provides the missing genetic information for treatment of the disease, and other elements, such as the promoter, that are used to express the gene in the target cells to provide the therapeutic benefit – are not implicated by the '617 patent. *See* Ex. 23 at 20:18-21:7; *see also* Ex. 24 at ¶¶ 43, 67.

Where there has been no showing that the Entire Market Value Rule should apply, Plaintiffs' damages expert must "'carefully tie proof of damages to the claimed invention's footprint in the market place.'" *See VirnetX,* 767 F.3d at 1329. The Federal Circuit has repeatedly emphasized the importance of apportionment as part of a district court's gatekeeping function. *See VirnetX,* 767 F.3d at 1328 (Fed. Cir. 2014) ("[T]he district court should have exercised its gatekeeping authority to ensure that only theories comporting with settled principles of apportionment were allowed to reach the jury."); *CSIRO,* 809 F.3d at 1301-02; *Ericsson, Inc. v. D-Link Sys., Inc.*, 773 F.3d 1201, 1226-27 (Fed. Cir. 2014). "A patentee is only entitled to a reasonable royalty attributable to the infringing features." *Power Integrations Inc. v. Fairchild Semiconductor Int'l Inc.*, 904 F.3d 965, 977 (Fed. Cir. 2018). "Whether 'viewed as valuable, important, or even essential,' the patented feature must be separated." *VirnetX,* 767 F.3d at 1329. Dr. Heeb's failure to separately value the patented technology, and exclude the value of unpatented features and functionality, renders his opinion unreliable and inadmissible. *Id.*

The Federal Circuit has "cautioned against reliance on the entire market value of the accused products" because of the danger of skewing the damages horizon, regardless of the contribution of the patented technology. *Id.* at 1327. *Uniloc* provides a "good example of the

danger" of admitting an un-apportioned royalty base "where the patented component does not create the basis for customer demand." 632 F.3d at 1320. In *Uniloc*, the patentee used defendant's $19.28 billion in revenue from the accused product as a "check." *Id.* at 1318-19. The Federal Circuit observed that "[a]s the district court aptly noted, '[t]he $19 billion cat was never put back into the bag even by Microsoft's cross-examination of [the patentee's expert] and re-direct of [its own expert], and in spite of a final instruction that the jury may not award damages based on Microsoft's entire revenue from all the accused products in the case.'" *Id.* at 1320. The Federal Circuit concluded that "[t]his is unsurprising." *Id.* "The disclosure that a company has made $19 billion dollars in revenue from an infringing product cannot help but skew the damages horizon for the jury, regardless of the contribution of the patented component to this revenue." *Id.*

Dr. Heeb's deposition testimony highlights the very danger about which *Uniloc* warns. At deposition, Dr. Heeb repeatedly asserted that, at the time of the hypothetical negotiation, Sarepta would have expected [redacted] in additional value from sales of SRP-9001 by taking a license and continuing development through the 35 months of the '617 patent term. *See, e.g.,* Ex. 23 at 52:1-4 ("Sarepta achieves [redacted] of additional value"), 75:16-18 ("the value of getting to market 35 months earlier is [redacted] 97:5-13 (getting to market 35 months sooner "will increase the value of [SRP-9001] by [redacted]."), 201:2-10 (SRP-9001 is "very valuable technology. . . Sarepta stands to earn [redacted] of profits in the future."). Here, the *Uniloc* concern is even greater because the [redacted] to which Dr. Heeb refers concern projected potential sales of final products, not realized revenues. *Id.* at 238:20-239:5. The admission of such projected values of overall profits at trial, "which have no demonstrated correlation to the value of the patented feature alone, only serve to make a patentee's proffered damages amount appear modest by comparison, and to artificially inflate the jury's damages calculation beyond that which is 'adequate to compensate for the infringement.'" *LaserDynamics, Inc.* 694 F.3d at 68.

Moreover, Dr. Heeb's reply report shows that he seeks to do what *Uniloc* teaches is improper – to present his proffered damages amount as a mere sliver of expected profits from the product to which the patented technology contributed. In *Uniloc*, the patentee's damages expert testified that his calculated royalty "accounted for only 2.9% of Microsoft's revenue, and accented his point by reference to a prepared pie chart, showing Microsoft's $19.28 billion in revenue with a 2.9% sliver representing his calculated royalty rate." *Uniloc*, 632 F.3d at 1318. In his reply report, Dr. Heeb similarly includes a pie chart showing the "share" of projected global SRP-9001 profits to each "involved party," under his licensing scenario. Ex. 21 at ¶ 112, Figure 2. According to Dr. Heeb, the projected "total global profits equal [redacted] (in net present value terms) and the reasonably [sic] royalty of [redacted] corresponds to a [redacted], [redacted]." *Id.* at ¶ 112. Just as the $19 billion "check" was improper in *Uniloc* (632 F.3d at 1319), Dr. Heeb's illustration of his proffered royalty as a percentage of global projected profits will serve only to skew the damages horizon for the jury.

The Court should exercise its gatekeeping authority and exclude Dr. Heeb's opinion based on his reliance on projected profits for SRP-9001 and his failure to "tie proof of damages to the claimed invention's footprint in the market place." *ResQNet.com,* 594 F.3d at 869.

B. Dr. Heeb Should be Precluded from Relying on Licenses that Are Not Comparable

Regenxbio has a history of licensing its portfolio of AAV patents, including the family of patents that contains the '617 patent (the "AAVrh10 patents"). *See, e.g.,* Ex. 20 at ¶¶ 37-58, 235. Dr. Heeb largely ignores the licenses that are limited to AAVrh10 patents in favor of other, non-comparable agreements with the highest potential payments.

It is well established that, for a damages expert to rely on a prior license, "there must be a basis in fact to associate the royalty rates used in prior licenses to the particular hypothetical

negotiation at issue in the case." *Uniloc*, 632 F.3d at 1317. "[L]icenses relied on by the patentee in proving damages [must be] sufficiently comparable to the hypothetical license at issue in suit." *Lucent*, 580 F.3d at 1325. "When relying on licenses to prove a reasonable royalty, alleging a loose or vague comparability between different technologies or licenses does not suffice." *LaserDynamics,* 694 F.3d at 79; *see also NNCrystal US Corp. v. Nanosys, Inc.*, No. CV 19-1307-RGA, 2023 WL 2891453, *3-4 (D. Del., April 11, 2023) (excluding testimony where expert failed to establish comparability of broader portfolio licenses); *M2M Solutions LLC v. Enfora, Inc.*, 167 F. Supp. 3d 665, 675-676 (D. Del. 2016) ("'The testimony of a damages expert in a patent suit who relies on non-comparable licenses in reaching his royalty rate should be excluded.'").

For example, in *ResQNet*, the patentee's expert relied on "re-bundling licenses" for "finished software products and source code, as well as services such as training, maintenance, marketing, and upgrades." *ResQNet*, 594 F.3d at 870. The Federal Circuit vacated the damages award, finding that the expert had relied on these non-patent license agreements with no "discernible link to the claimed technology" in order to impermissibly "drive the royalty rate up to unjustified double-digit levels." *Id.* As the Federal Circuit explained, licenses must be "commensurate with what the defendant has appropriated. If not, a prevailing plaintiff would be free to inflate the reasonable royalty analysis with conveniently selected licenses without an economic or other link to the technology in question." *Id.* at 872. Upon remand, the trial court was instructed to "not rely on unrelated licenses to increase the reasonable royalty rate above rates more clearly linked to the economic demand for the claimed technology." *Id.* at 872-73.

Similarly, in *LaserDynamics*, the Federal Circuit found that the trial court erred in admitting a license agreement "where comparability between it and a hypothetical license to [the patent-in-suit] was absent." *LaserDynamics,* 694 F.3d at 80. That license did not involve the patent-in-suit, and no evidence showed that it involved the relevant technology. *Id.* There, as

here, reliance on an irrelevant license "to the exclusion of the many licenses expressly for the [patent-in-suit] served no purpose other than to 'increase the reasonable royalty rate above rates more clearly linked to the economic demand for the claimed technology.'" *Id.*

Dr. Heeb's Table 1 summarizes [redacted] that he describes as "informative of the hypothetical license." Ex. 20 at p. 31. Two of the summarized agreements were limited to AAVrh10 patents. *See id.* Those licenses include [redacted] same family. *See id.* at ¶¶ 41, 47, *see also* Ex. 24 at Ex. 9. Several other listed licenses cover multiple specified vectors, including AAVrh10. Ex. 20 at p. 31. The licenses with [redacted] noted in the "Vectors" column cover [redacted]. *See id; see also* Ex. 23 at 157:4-12. Dr. Heeb's summary of "informative" agreements also includes a collaboration agreement between Regenxbio and [redacted] that is limited to [redacted] in this case. Ex. 20 at p. 31; Ex. 23 at 116:1-11.[3] Dr. Heeb contends that the [redacted] agreement, along with the [redacted], are "most relevant to the considerations of negotiators at a hypothetical negotiation." Ex. 20 at ¶ 235. However, Dr. Heeb does not contend that these agreements are "comparable," nor can he. *See* Ex. 21 at ¶ 46 (stating that the [redacted] agreements are "not 'comparable licenses,'"); *see also* Ex. 23 at 117:18-120:10. The fact that Dr. Heeb cherry-picked two Regenxbio agreements with the [redacted] economic value, to the exclusion of licenses more closely tied to the AAVrh10 patents, serves no purpose other than to try to inflate the royalty rate, and his resulting opinions should be excluded.

The [redacted] agreement is neither technologically nor economically comparable to the hypothetical license. To begin, the [redacted] agreement does not

[3] Dr. Heeb ignores numerous Regenxbio licenses ostensibly because they do not include rh.10. *See* Ex. 24 at Ex. 10. Yet, Dr. Heeb relies on the [redacted] Agreement – which concerns [redacted] – confirming the Dr. Heeb selectively relied on non-rh.10 agreements when it suited his purpose of improperly driving up the royalty rate.

cover the '617 patent. Ex. 20 at p. 31; Ex. 23 at 116:1-11. Moreover, the [redacted] agreement is a collaboration agreement that concerns [redacted]. Specifically, the [redacted] agreement grants [redacted]. Ex. 20 at ¶¶ 34, 57. The [redacted] agreement grants [redacted]. Ex. 20 at ¶ 57, *see also* Ex. 24 at ¶ 99. The patent rights under the [redacted] agreement include [redacted]. Ex. 24 at ¶ 101; Ex. 25 at ¶¶ 107-120. The [redacted] agreement is not structured with a single, upfront lump sum royalty, but instead includes [redacted]. Ex. 20 at p. 31 (Table 1). Further, "Regenxbio had already [redacted]" when the parties entered the [redacted] agreement. *Id.* at ¶ 57.

[redacted], the hypothetical license would be a non-exclusive license to the '617 patent alone. *See* Ex. 23 at 12:9-13:18. Dr. Heeb concedes that "[t]he particular rights that are being conveyed [by the [redacted] Agreement] are not similar and they are not sufficiently similar to use just that [redacted] license or even several licenses like it in order to deduce the reasonable royalty." *Id.* at 93:6-94:9. Nonetheless, Dr. Heeb contends that the [redacted] agreement tells "the nature of the negotiation between two firms over rights for a product that is that valuable." *Id.* at 93:6-94:9. Dr. Heeb's opinion improperly relies on a non-comparable agreement which he likens to the projected value of SRP-9001, not to the value of the patented technology that is the subject of the hypothetical license. *See id* at 96:18-97:4.

The second agreement Dr. Heeb considers most relevant, the [redacted] is also not comparable. In [redacted] Regenxbio granted [redacted]

[redacted] Ex. 20 at ¶ 43. In [redacted], Regenxbio and [redacted]. *Id.* at ¶ 44. One significant aspect of the [redacted]. Ex. 24 at ¶ 111. [redacted]. Ex. 20 at ¶¶ 44-45; Ex. 24 at ¶ 113. A second significant aspect of the [redacted] was that it granted [redacted], [redacted]. Ex. 20 at ¶ 44; Ex. 24 at ¶ 113. These [redacted] a significant competitive advantage because no other company would be able to [redacted]. Ex. 24 at ¶ 113, *see also* Ex. 23 at 159:11-160:16; 165:15-166:1. At the time of the [redacted]. Ex. 20 at ¶¶ 45-46. Further, like the [redacted] agreement, and like most of Regenxbio's licenses, the [redacted]. Ex. 20 at ¶¶ 43-44, p. 31 (Table 1). Neither the scope of licensed rights, nor the circumstances of the parties, are comparable to the hypothetical negotiation concerning a non-exclusive license to a single patent.

Dr. Heeb's third "most relevant" license is Sarepta's License, Collaboration, and Option agreement with F. Hoffman La Roche (the "Roche Agreement"). As with the [redacted] agreements, Dr. Heeb makes no showing that the Roche agreement is either technologically or economically comparable to the hypothetical license, and it is not. The Roche Agreement does not concern rights to Regenxbio's '617 patent. Ex. 20 at ¶ 138. It is a license, collaboration, and

option agreement that, among other things, gives Roche exclusive rights to commercialize SRP-9001 outside of the United States. Ex. 20 at ¶ 30; Ex. 23 at 101:22-103:13. The Roche Agreement grants Roche ex-US rights to all [redacted]. Ex. 24 at ¶ 121. Under the Roche Agreement, Sarepta [redacted]. Ex. 24 at ¶ 121. The agreement also grants Roche [redacted]. *Id.* Roche's $1.15 billion in upfront payments included a [redacted]. *Id.* at ¶ 122; Ex. 20 at ¶ 30. Dr. Heeb's reliance on the non-comparable Roche Agreement is another example where he relies on the total value of the SRP-9001 product, instead of the value attributable to the patented technology, to artificially inflate the royalty amount.

Dr. Heeb acknowledges that, without showing comparability, he uses the [redacted], and Roche agreements to "corroborate the general magnitude of the royalties in these different agreements." Ex. 21 at ¶ 49. That is improper. There is no basis to allow reliance on incomparable licenses as a "sanity check." *M2M Solutions*, 167 F. Supp. 3d at 678. Rather, "Federal Circuit precedent requires that for a license to be used in a damages analysis, the license must be proven comparable to the hypothetical negotiation." *Id.* None of the [redacted], or Roche agreements are comparable to the hypothetical negotiation or "commensurate with" the patented technology, and Dr. Heeb admits that he does not even attempt to make such a showing. Thus, Dr. Heeb's reliance on these agreements is an improper attempt to "inflate the reasonable royalty analysis with conveniently selected licenses without an economic or other link to the technology in question," and should be excluded. *ResQNet*, 594 F.3d at 872.

C. Dr. Heeb's Methodology for Dividing Projected "Surplus" Between the Negotiating Parties Is Unreliable and Untethered to the Facts of This Case

As discussed above, Dr. Heeb's analysis begins with his calculation of the difference between Sarepta's projected profits for SRP-9001 if it launched on the anticipated schedule as of

the hypothetical negotiation and the potential profits if the anticipated launch date were delayed by 35 months. Dr. Heeb also calculates a "minimum willingness to accept" ("MWA") value for Regenxbio, based on the difference in value of Regenxbio's [redacted], adjusted for risk, in each of the "license" and "no license" to Sarepta scenarios. According to Dr. Heeb, the MWA value "exactly compensates Regenxbio for the [redacted] if Sarepta were permitted to develop its DMD product during the period from January 2020 through November 2022." Ex. 20 at ¶ 190. After correcting for an error in his earlier calculations, the amount that would "exactly compensate" Regenxbio for [redacted] if Sarepta continued to develop its product during the 35 month period is [redacted]. Ex. 21 at ¶ 21, 23. Dr. Heeb's "bargaining range" is therefore from [redacted], resulting in a calculated "surplus" of [redacted]. Ex. 21 at ¶ 23, Figure 1.

After calculating his bargaining range, Dr. Heeb applies three bargaining models to divide the range. Courts have cautioned that an expert may rely on economic models to predict the outcome of hypothetical negotiations only if the expert establishes that the theorem actually applies to the facts of the case. *See VirnetX,* 767 F.3d at 1332 (rejecting a model because "[i]t itself asserts nothing about what situations in the real world fit [its] premises" and stating that "[a]nyone seeking to invoke [a] theorem as applicable to a particular situation must establish that fit"). Because Dr. Heeb has not established the necessary fit between the bargaining models he applies and the facts of this case, his opinion concerning the division of the bargaining range should be excluded.

Dr. Heeb first applies the Rubenstein model, which he describes as a "canonical bargaining model in the economic literature of game theory." Ex. 20 at ¶ 196. In the Rubenstein model, "the relative bargaining power of the parties is represented by their respective discount rates, a measure of their patience." *Id.* Dr. Heeb obtained the discount that he used for Sarepta from Bloomberg. *Id.* at ¶ 197. In *Limelight Networks, Inc. v. XO Commc'n, LLC*, the Eastern District of Virginia

considered application of the Rubenstein model using each side's weighted average cost of capital ("WACC") as a proxy for their patience. No. 3:15-CV-720-JAG, 2018 WL 678245, *3 (E.D. Va., Feb. 2, 2018). As that court noted, using WACC as a proxy, "the model would split any negotiation between the parties in the same way, no matter the stakes." *Id.* So too here, reliance on Sarepta's overall discount rate in this model has no connection to the '617 patent. Dr. Heeb concedes that Rubinstein "is not influenced by the particulars of the technology that is transferred." Ex. 23 at 221:21-222:2. Dr. Heeb also acknowledges that Rubinstein is not a good fit for the facts of this case as Rubinstein is a "particularly good predictor of the division of surplus when patience of the parties tends to drive the outcome of the negotiation" but "[t]he current situation involves negotiations between two sophisticated parties that are unlikely to be influenced by such concerns." Ex. 20 at ¶ 211. Even so, Dr. Heeb contends that the Rubinstein model has "some application" here, and he assigns this method 1/9 weight in dividing the bargaining range. *Id.*

The second model Dr. Heeb applies is Shapley. Ex. 20 at ¶ 199. Dr. Heeb describes Shapley as "a stalwart theoretical mechanism used in the economics literature on cooperative game theory to divide the value of an agreement (called a 'coalition' in this literature), based on the marginal contribution of each party to the coalition." *Id.* Dr. Heeb's application of the Shapley method involved calculating the parties' "marginal contributions" to the "total value of the coalition" based on [redacted] *Id.* at ¶¶ 201-203. Accordingly, the Shapley methodology relies entirely on the value of projected profits from approved gene therapy products, and is not tailored to the contribution of the patented technology. As with the Rubenstein model, Dr. Heeb acknowledges that Shapley is not a good fit, but he assigns it 2/9 weight nonetheless. *Id.* at ¶¶ 212, 215.

Dr. Heeb's third model is the Total Contributions method, which he states "reflects equity concerns and incorporates all of the contributions of the parties including contributions made in

the past." *Id.* at ¶ 213. According to Dr. Heeb, the "Total Contributions method sums all contributions made by each party that were necessary to construct the value that is shared in the negotiation. . . . This ensures that each party is rewarded for all of its contributions, not just those that are incrementally valuable." *Id.* at ¶ 214. Dr. Heeb further states that, in his opinion, the "Total Contributions method should generally receive at least as much weight as the Shapley method, and more if the other methods do not reflect all the important circumstances of the particular negotiation." *Id.* at ¶ 215. Also, if there is a substantial difference between Shapley and Total Contributions, there is a concern that the solution is not "fair." *Id.* According to Dr. Heeb, putting "more weight" on Total Contributions alleviates the fairness concern "and is therefore also more predictive of the outcome vis-à-vis real world negotiations." *Id.* Dr. Heeb then assigns the Total Contributions model 6/9 weight, rather than using only this model, notwithstanding that it is "more predictive" of the outcome of real-world negotiations. *Id.* at ¶¶ 215-216.

Here, as in *Virnetx*, the Court should reject the use of bargaining solutions where the expert failed to fit the assumptions underlying the model to the facts of the case. *See Virnetx,* 767 F.3d at 1332-33. Moreover, similar to *Virnetx*, Dr. Heeb's weighting of the bargaining solutions shows how application of these methods may be artificially manipulated. In *Virnetx* the expert's "thin attempts to explain his 10% deviation from the 50/50 baseline" illustrates "how this methodology is subject to abuse." *Id.* at 1333. The expert there testified that "although he 'considered other splits,' he ultimately determined that a 10% deviation – resulting in a 45/55 split – was appropriate 'to reflect the fact that [defendant] would have additional bargaining power over [plaintiff]." *Id.* Such "conclusory assertions" from an expert "cannot form the basis of a jury's verdict." *Id.*

When Dr. Heeb was asked at his deposition how he arrived at the weights for each of the three bargaining models, his initial answer spanned more than six pages. Ex. 23 at 205:10-212:3. When then asked about his "methodology" used to determine the weight assigned to each

bargaining model, he continued for several more pages. *See id.* at 212:4-216:5. Ultimately, he testified that his weighting of the three models comes down to his "judgment" as a professional expert. *See id.* at 217:19-218:12. Dr. Heeb could have assigned different weights to each model, with significantly different results each time. Table 6 to the Heeb Reply Report demonstrates five different sets of weights applied to the three models, resulting in calculated royalty values ranging from [redacted]. Ex. 21 at Table 6 (page 86). In these alternative scenarios, the greatest weight that Dr. Heeb applied to the Total Contributions method was [redacted] as shown in the third set of weights. *Id.* As Ms. Mulhern explains, relying [redacted] on the Total Contributions method results in a royalty of [redacted]. Ms. Mulhern shows the significant range of potential royalties available if one applies Dr. Heeb's faulty method and arbitrary judgment as to the weight assigned to each approach. Ex. 26. Dr. Heeb's method, including its overinflated royalty base of projected profits for the SRP-9001 product, is unreliable and should be excluded in its entirety. *See Uniloc*, 632 F.3d at 1321 (a damages award may not be supported by a "faulty foundation.").

IX. DR. LEONE'S OPINIONS ON SAREPTA'S KNOWLEDGE AND ALLEGED INTENT SHOULD BE EXCLUDED

"It is well settled that experts may not provide testimony concerning 'the state of mind' or 'culpability' of defendants[.]" *Shire Viropharma Inc. v. CSL Behring LLC*, No. CV 17-414, 2021 WL 1227097, at *5-6 (D. Del. Mar. 31, 2021). "Expert testimony as to intent, motive, or state of mind offers no more than the drawing of an inference from the facts of the case and permitting expert testimony on this subject would be merely substituting the expert's judgment for the jury's and would not be helpful . . ." *Zimmer Surgical, Inc. v. Stryker Corp.*, 365 F. Supp. 3d 466, 497 (D. Del. 2019); *see also Sonos, Inc. v. D & M Holdings Inc.*, 297 F. Supp. 3d 501, 521–22 (D. Del. 2017) (precluding party from "invoking the special imprimatur that accompanies [evidence's] presentation by an expert" when the jury could draw its own inferences). Such testimony directly implicates the Court's gate-keeping role under *Daubert*.

Here, Dr. Leone purports to offer "opinions" on Sarepta's knowledge of the '617 patent and alleged intent to induce and/or contribute to infringement. Ex. 4 at ¶¶ 298-304. Her "analysis" of these issues amounts to a summary of certain documents and testimony that Plaintiffs have relied on in support of their indirect infringement claims. *Id.* at ¶¶ 295-298, 300-302. The jury is fully equipped to review documents, assess the credibility of witnesses, weigh evidence, and make their own determinations on issues of Sarepta's knowledge and alleged intent without Dr. Leone's second-hand commentary.

Dr. Leone's testimony at her deposition confirms that her "opinions" on these issues provide no assistance on any technical issue. Ex. 10 at 291:10-315:20. Instead, Dr. Leone is merely expressing her personal opinions regarding the weight of certain evidence and the inferences that she believes the jury should draw as to what Sarepta "must have" known or intended. *Id.* at 299:18-301:20, 306:9-307:12, 307:14-308:23, 313:8-315:20.

These are exactly the types of "opinions" that fall squarely within *Daubert*, and should be excluded. *See, e.g.*, *AstraZeneca LP v. Tap Pharm. Prod., Inc.*, 444 F. Supp. 2d 278, 293 (D. Del. 2006); *f'real Foods, LLC v. Hamilton Beach Brands, Inc.*, No. CV 16-41-CFC, 2019 WL 1578259, at *1 (D. Del. Apr. 11, 2019) (precluding opinions on intent that were untied "to the technical analysis [expert] offers and for which [expert] has specialized knowledge," when instead "[t]hose facts should be presented through fact witnesses and/or documents").

X. CONCLUSION

Sarepta respectfully requests that the Court (1) enter summary judgment of no infringement as to all Asserted Claims, (2) enter summary judgment that all Asserted Claims are invalid for lack of patentable subject matter, and (3) exclude the expert opinions of Dr. Heeb on damages and Dr. Leone on indirect infringement as unreliable under *Daubert* and Fed. R. Evid. 702.

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August 25, 2023

CERTIFICATE OF SERVICE

I hereby certify that on August 25, 2023, I caused the foregoing to be electronically filed with the Clerk of the Court using CM/ECF, which will send notification of such filing to all registered participants.

I further certify that I caused copies of the foregoing document to be served on August 25, 2023, upon the following in the manner indicated:

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